REMARKS

Applicants submit this Amendment in response to the Office Action of November 4, 2003. The claims have been amended as follows.

Claim 54 has been amended to correct an obvious error, as indicated by the Examiner in the Office Action on page 2. Claims 47 and 59 have been amended to change dependency. Claims 82 to 90 have been added. Support for these new claims is found in the specification on page 13, lines 1 to 18.

WITHDRAWAL FROM CONSIDERATION OF CLAIMS 74 TO 79

The Examiner has withdrawn claims 74 to 79 as being directed to an invention that is distinct from the invention that was originally claimed. The Examiner bases this holding on the fact that claims 74 to 79 are drawn to an enhancement of the solubilizing effect of BCD, per se which the Examiner states is separate from what has already been examined. Applicants traverse this holding of the Examiner and request that claims 74 to 79 be examined presently.

Claim 74, and claims 75 to 79 which are dependent from claim 74, call for enhancement of the solubilizing effect of BCD *on the solubility of metronidazole in aqueous fluid*. The features of the claim are combining either niacin or niacinamide with the BCD. Applicants submit that the invention of this claim is not distinct from the other claims that are presently examined, such as that of claim 63. Claims 63 and 74 call for the same limitations of combining BCD, water, and either niacin or niacinamide. Applicants submit that it is not reasonable to state that claim 74 and claim 63, which claims call for the same limitations, are

distinct and independent. Accordingly, Applicants request the Examiner to withdraw this finding and to presently examine claims 74 to 79.

OBJECTIONS TO THE CLAIMS

The Examiner has objected to claim 54 because the claim recites "1/0%". The claim has been corrected to recite "1.0%" which was originally intended by applicants. as being a duplicate of claim 21. Applicants request the Examiner to withdraw this objection to this claim.

REJECTIONS OF THE CLAIMS

I. Rejections under 35 U.S.C. §112, second paragraph.

A. The Examiner has rejected claim 47 as being indefinite for its dependency from claim 46. Claim 47 has been amended to correct the dependency of this claim. As amended, claim 47 depends from claim 45, as was originally intended by Applicants. Accordingly, Applicants submit that this basis of rejection has been overcome and request the Examiner to withdraw the rejection of this claim on this ground.

B. The Examiner has rejected claim 59 as being indefinite for its dependency from canceled claim 1. In the present Amendment, Applicants have amended claim 59 to depend from claim 45. Accordingly, Applicants submit that this basis of rejection has been overcome and respectfully request the Examiner to withdraw the rejection of this claim on this ground.

II. Rejections under 35 U.S.C. §103

A. Kata, Acta Pharm. Hung, 54:116-122 (1984), and Chien, U.S. Patent No. 4,032,645

B. Kata, Acta Pharm. Hung, 54:116-122 (1984), Chien, U.S. Patent No. 4,032,645, and Czernielsewski, U.S. Patent No. 5,849,776

C. Kata, Acta Pharm. Hung, 54:116-122 (1984), Chien, U.S. Patent No. 4,032,645, and Loftsson, U.S. Patent No. 5324,718

The Examiner has rejected claims 24, 27-29, 31, 32, 40, 41, 43-58, 63, 65-68, 71-73, 80, and 81 as being obvious in view of the combined disclosure of Kata, Acta Pharm. Hung, 54:116-122 (1984), and Chien, U.S. Patent No. 4,032,645. The Examiner has rejected claims 26, 30, 33-39, 42, 59-62, 64, and 70 as being obvious in view of the combined disclosure of Kata, Chien, and Czernielsewski, U.S. Patent No. 5,849,776. The Examiner has rejected claims 25 and 69 as being obvious in view of the combined disclosure of Kata, Chien, and Loftsson, U.S. Patent No. 5324,718. Applicants traverse the rejections of the claims on these grounds.

1. The Examiner has failed to establish a prima facie case of obviousness of the claims in view of the prior art

A. Applicants submit that the prior art does not disclose or suggest the combination of betacyclodextrin, metronidazole, and nicotinamide (niacinamide) as is presently claimed. Kata discloses aqueous solutions comprising betacyclodextrin and metronidazole. Kata does not disclose nicotinamide. Chien discloses that the solubility of metronidazole in water may be increased by including ethanol and N,N-dimethylacetamide in the water. Chien further discloses that the concentration of N,N-dimethylacetamide needed in combination with ethanol to obtain a

particular concentration of metronidazole may be decreased by substituting niacinamide for a portion of the N,N-dimethylacetamide. There is no disclosure in Chien of increasing the solubility of metronidazole in water without using both ethanol and N,N-dimethylacetamide.

Applicants submit that there is no teaching in the prior art to utilize niacinamide without ethanol and N,N-dimethylacetamide to increase the solubility of metronidazole in water. Applicants further submit that there is no teaching in the prior art of using nicotinamide, either by itself or in combination with ethanol or N,N-dimethylacetamide, in combination with betacyclodextrin to increase the solubility of metronidazole in water. Combining the Kata and Chien references does not suggest the present invention. Although Applicants submit that the references cannot be combined as follows, it is submitted for argument sake that, at most, the combination of Kata and Chien might be construed to suggest the combination of betacyclodextrin (from Kata) with ethanol, N,N-dimethylacetamide, and niacinamide (Chien) with metronidazole in water. Thus, Applicants submit that the Examiner has failed to establish a prima facie case of obviousness of claims 24, 27-29, 31, 32, 40, 41, 43-58, 63, 65-68, 71-73, 80, and 81 over the combined disclosure of Kata and Chien. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection of these claims on this ground.

B. The Czernielewski patent discloses aqueous metronidazole gels for treatment of dermatologic conditions. Czernielewski does not disclose betacyclodextrin, niacinamide, or niacin. The Examiner has cited this reference against several dependent claims which claim additional features not disclosed in the primary references, Kata and Chien.

However, the teaching of Czernielewski does not fill in the gaps in the teachings of the Kata and Chien references regarding the combination of niacinamide and betacyclodextrin pertaining to the solubility of metronidazole in water. Thus, Applicants respectfully submit that the combination of Kata, Chien, and Czernielewski is insufficient for a prima facie case of obviousness of the inventions called for in claims 26, 30, 33-39, 42, 59-62, 64, and 70. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection of these claims on this ground.

C. Loftsson discloses methods for enhancing the solubility enhancing property of a cyclodextrin by combining it with a water-soluble polymer. Such combination may be used to solubilize metronidazole. Loftsson discloses that the increased drug solubility enhancement of the cyclodextrin/polymer combination is due to the formation of a complex involving the drug, the cyclodextrin, and the polymer. See column 12, lines 33 to 46.

There is no disclosure or suggestion in the prior art that betacyclodextrin and either niacinamide or niacin for such complexes, which complexes are necessary for the enhanced solubility of drugs when combining a cyclodextrin and the polymer of Loftsson. Accordingly, Applicants submit that the combination of Kata, Chien, and Loftsson does not disclose or suggest the inventions called for in claims 25 and 69. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection of these claims on this ground.

2. Even if a prima facie case of obviousness is established, the present claims are patentable over the prior art

Assuming arguendo that the Examiner has established a prima facie case of obviousness of the claims based on the combined disclosures of Kata and Chien or of Kata and Chien in combination with either Czernielewski or Loftsson, the present claims are patentable because the combination of betacyclodextrin and nicotinamide or niacin produces unexpected advantageous properties pertaining to the aqueous solubility of metronidazole. Such unexpected advantageous properties are disclosed in the specification as follows.

a. The maximum solubility of metronidazole in aqueous solution without additional solubility enhancers is 0.7% w/w.

b. Inclusion of betacyclodextrin (BCD) at its maximum aqueous solubility, that is at 0.5% w/w, provides a solubility of metronidazole of 0.8%. Thus, 0.5% BCD increases the solubility of metronidazole by 0.1% above baseline.

c. Inclusion of niacinamide at a concentration of 3% is required to increase the solubility of metronidazole in water to 1%. Thus, 3% niacinamide increases the solubility of metronidazole by 0.3% above baseline.

d. Inclusion of BCD at a concentration of 0.5% and niacinamide at a concentration of 1% increases the solubility of metronidazole by 0.3%.

e. If this data showed only the additive effects of 0.5% BCD and 1% niacinamide, one would expect a maximum solubility of metronidazole of 0.9%. 0.1% is due to BCD and another 0.1% (one third of the solubility increase that one would expect from the data showing that 3% niacinamide raises the solubility of metronidazole by 0.3%). Thus, additive

solubility enhancement by 0.5% BCD and 1% niacinamide would provide an aqueous solubility of metronidazole in water of 0.9%, or an increase of 0.2% over baseline.

However, the combination of 0.5% BCD and 1% niacinamide produces a solubility of metronidazole in water of 1%, which is 0.3% over baseline. This level is a 50% increase in metronidazole solubility compared to baseline over that which one would expect if the results of combining BCD and niacinamide were just additive. This data establishes synergy of niacinamide and BCD in solubilizing metronidazole in water.

Similar data is shown for niacin in combination with BCD.

Niacin is a more efficient solubility enhancing agent than is niacinamide, as shown in the data in Table 5 on page 14 of the specification. A concentration of niacin of 0.75% w/w provides an enhancement in aqueous metronidazole solubility to obtain a stable 1% aqueous metronidazole solution. Further, as shown in Table 6 on page 15, 0.5% niacin, which is only two/thirds of the concentration needed to obtain a stable 1% metronidazole solution, may be combined with 0.5% BCD to obtain a stable 1% aqueous metronidazole solution.

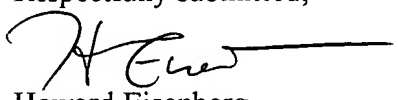
Applicants submit that the above data establishes synergy of BCD in combination with either niacinamide or niacin and that such synergy is sufficient to overcome the rejection of the claims on the grounds of obviousness. Accordingly, the Examiner is requested to withdraw the rejection of the claims on this ground.

Applicants further submit that, if the Examiner is not convinced that the data in the specification establishes such synergy, Applicants are presently preparing an additional study to establish synergy and will submit such data in a future declaration.

CONCLUSION

Applicants submit that the claims are in condition for allowance. The Examiner is requested to withdraw all present grounds for rejection of the claims and to promptly issue a notice of allowance. Applicants submit herewith a Request for Continued Examination of the application.

Respectfully submitted,



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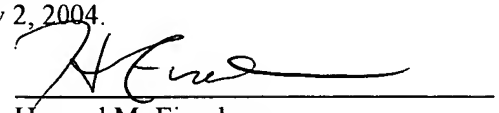

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